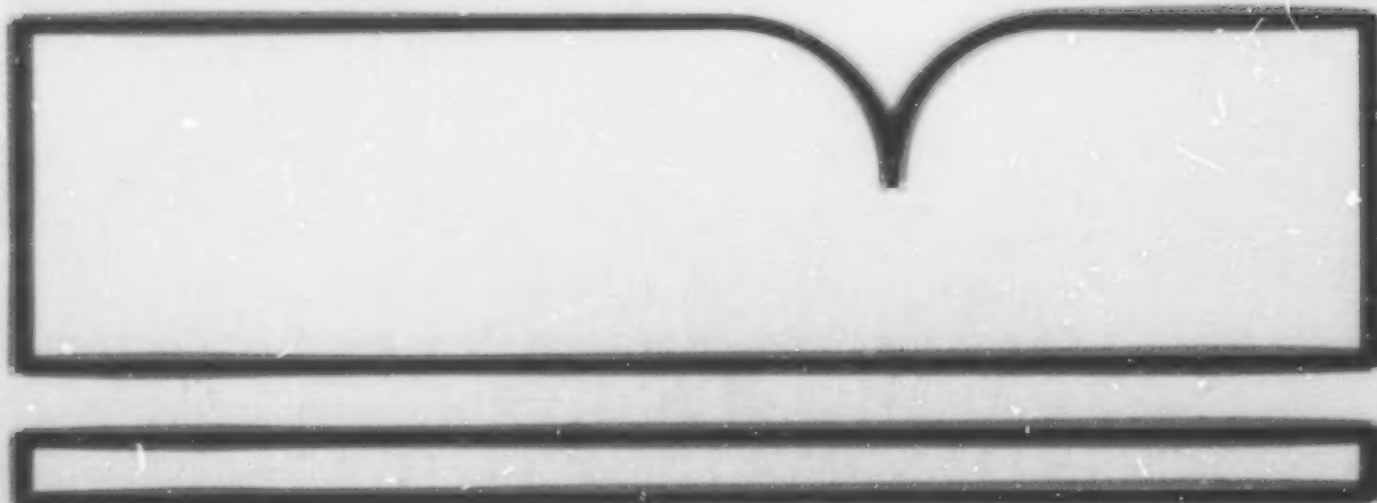


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Health Effects Assessment for
Vanadium and Compounds

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jul 87



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HEALTH EFFECTS ASSESSMENT
FOR VANADIUM AND COMPOUNDS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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16. ABSTRACT This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfDs or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q1*s have been computed, if appropriate, based on oral and inhalation data if available.		
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PREFACE

This report presents a brief summary and evaluation of information relevant to a preliminary interim assessment of adverse health effects associated with vanadium and compounds. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1983a. Reportable Quantity Document for Vanadyl Sulfate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for Vanadium (V) Oxide (Vanadium Pentoxide). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Vanadium Pentoxide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for vanadium pentoxide. Online. (Verification date 2/26/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the available data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfDs (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFDs estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RFD_{SI}) and oral (RFD_{SO}) exposures.

The RFD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RFD is route-specific and estimates acceptable exposure for either oral (RFD_O) or inhalation (RFD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RFDs and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. For carcinogens, q₁'s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Several subchronic and chronic oral studies in animals with various compounds of vanadium were found in the available literature. A 90-day drinking water study using rats with sodium metavanadate indicated that this compound is more toxic than vanadium pentoxide or vanadyl sulfate (Domingo et al., 1985). A NOAEL of 0.55 mg vanadium/kg/day, associated with mild lesions in lungs, spleen and kidney in this study, was used as the basis of an RFD_{SO} for vanadium of 0.4 mg/day. The RFD_{SO} for sodium vanadate is 1 mg/day for a 70 kg human. In the absence of suitable subchronic studies for vanadium pentoxide and vanadyl sulfate, the RFD_O from chronic studies can be adopted as an RFD_{SO}. The RFD_O for sodium vanadate can be obtained from the RFD_{SO} by using an additional uncertainty factor of 10 to account for extrapolation of subchronic study to chronic. This RFD_O is 0.1 mg/day for a 70 kg human. The RFD_O for vanadium pentoxide can be obtained from chronic dietary study (Stokinger, 1981). A NOAEL of 10 ppm of vanadium in diet corresponds to 18 ppm of vanadium pentoxide and an RFD_O of 0.009 mg/kg/day or an RFD_O of 0.6 mg/day for vanadium pentoxide. The RFD_O for vanadium sulfate can be obtained from chronic water intake study in rats and mice (Schroeder and Mitchener, 1975); 5 ppm of vanadium in water corresponds to a vanadium intake of 0.9 mg/kg/day in rats and 0.7 mg/kg/day in mice. The RFD_O is obtained by using an uncertainty factor of 100. A more conservative value in mice corresponds to an RFD_O for vanadium of 0.5 mg/day or an RFD_O for vanadyl sulfate of 1.6 mg/day. The most conservative RFD_O of 0.04 mg/day vanadium can then be obtained from the RFD_O for sodium vanadate. This number may be overly conservative since it is more than an order of magnitude smaller than the RFD_O for vanadium obtained from the chronic studies.

Data were insufficient to derive RFD_{SI} or RFD_I values for vanadium or its compounds. Vanadium appears to be more toxic by inhalation than by ingestion. The maximum CS of 32.9 for vanadium was based on persistent cough, dyspnea and wheezing in humans exposed to vanadium pentoxide at 0.02-3.2 mg/m³ occupationally for 8 years.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RBC	Red blood cell
RfD	Reference dose
RfD _I	Inhalation reference dose
RfD _O	Oral reference dose
RfD _{SI}	Subchronic inhalation reference dose
RfD _{SO}	Subchronic oral reference dose
RMCL	Recommended maximum contamination levels
RV _d	Dose-rating value
RV _e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average
WBC	White blood cell

1. ENVIRONMENTAL CHEMISTRY AND FATE

Vanadium is a metal that is a member of the first transition series of the Periodic Table. Vanadium is widely distributed in low abundance throughout the earth's crust and is also found in trace amounts in fossil fuels. The lithosphere contains ~0.01 wt% vanadium and few deposits contain >1-2 wt% of this element. Vanadium has oxidation states of +2, +3, +4 and +5 (Baroch, 1983), and usually occurs in some oxidized form such as metal vanadate (NLM, 1986). Physical properties of vanadium and some of its compounds are presented in Table 1-1.

In water, vanadium can exist in both soluble forms and as a precipitate. Vanadium deposited in water by wet and dry deposition may reenter the atmosphere as sea salt aerosol particles generated at ocean surfaces (Arimoto et al., 1985). Monitoring data that show at least 100-fold higher concentration of vanadium in sediment than in aqueous solution indicate that vanadium can precipitate out of solution and accumulate in sediments. Vanadium from water can be taken up and accumulated by fish. BCFs of 365-630 were observed in different fish (Sadiq and Zaidi, 1985; Heit et al., 1984; Tsui and McCart, 1981).

It is reported that vanadium in the air is solely a result of industrial processes. For example, in the lower Delaware River valley, the principal sources are emissions from the combustion of vanadium-rich fuel oils in refineries, power plants and other industries. A secondary source is particulate emissions from the catalytic processing of petroleum in refineries. Upon emission during combustion, vanadium oxides combine into particulate fly ash. Lower oxides of vanadium will ultimately oxidize to V_2O_5 , especially at the high temperatures encountered in combustion

TABLE 1-1

Physical Properties of Vanadium and Some of Its Compounds*

Compound	CAS Number	Molecular Formula	Atomic/Molecular Weight	Form	Melting Point (°C)	Boiling Point (°C)	Water Solubility (mg/l)
Sodium metavanadate	13718-26-8	NaVO ₃	121.93	yellowish-white crystalline powder	NA	NA	soluble in hot water
Vanadium	7440-62-2	V	50.94	light gray cubic, metal	1890±10	3380	insoluble
Vanadium carbide	12070-10-9	VC	62.95	black, cubic	2810	3900	insoluble
Vanadium dioxide	12036-21-4	VO ₂ (or V ₂ O ₄)	82.94	blue, crystalline	1967	NA	insoluble
Vanadium nitride	24646-05-3	VN	64.95	black, cubic	2320	NA	insoluble
Vanadium oxide	12035-98-2	VO (or V ₂ O ₃)	66.94	light gray, crystalline	ignites	NA	insoluble
Vanadium pentoxide	1314-62-1	V ₂ O ₅	181.88	yellow-red, rhombic	690	decomposes 1750	8000 (20°C)
Vanadium sulfate	36907-42-3	VSO ₄ ·7H ₂ O	273.11	violet, monocyclic	decomposes in air	NA	NA
Vanadium tetrachloride	7632-51-1	VC1 ₄	192.75	red-brown, liquid	-20±2	148.5 at 755 mm Hg	soluble, decomposes
Vanadium trioxide	1314-34-7	V ₂ O ₃	149.88	black, crystalline	1970	NA	slightly soluble
Vanadium trisulfide	1315-03-3	V ₂ S ₃	198.06	green-black, plates or powder	decomposes >600	NA	insoluble

*Source: Weast, 1965

NA = Not available

stacks (100-500°C). Vanadium pentoxide may also exist in equilibrium with sulfur and compounds resulting from stack reactions with SO_2 . The residence time of vanadium in the atmosphere has been estimated to be 0.36 day. Deposition is the only likely sink for the vanadium emissions. It was estimated using Stoke's law for settling rates that the residence time of the fly ash vanadium pentoxide/ H_2SO_4 aerosols should be ~1 day. Rainout would be expected to be an additional mechanism for removal from air (U.S. EPA, 1985a).

The half-lives of vanadium and its compounds in soil could not be located in the available literature. Vanadium pentoxide is sufficiently soluble in water (8000 mg/L at 20°C) to indicate potential for soil mobility by leaching. It is possible that leaching may be hindered by the formation of chemical complexes between vanadium and soil constituents. Vanadium pentoxide/ H_2SO_4 that may deposit on soil from the atmosphere will be transported to natural waters by runoffs (U.S. EPA, 1985a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

In humans, ingested vanadium is absorbed poorly by the gastrointestinal tract. Only 0.1-1.0% of a 100 and 125 mg dose of diammonium oxytartarovanadate was absorbed gastrointestinally, and 60% of the absorbed dose was excreted by the kidneys within 24 hours (Curran et al., 1959). Only $2.6 \pm 1.6\%$ of the radioactivity from a 0.3 mg/kg dose of vanadium from $^{51}\text{V}_2\text{O}_5$ administered by gavage was absorbed by 70-day-old female Fischer rats (Conklin et al., 1982). Dimond et al. (1963) administered orally to humans, tablets containing 25 mg of ammonium vanadyl tartarate 1-4 times/day. Six subjects were treated for 45-68 days. Varying amounts of vanadium were excreted in the urine, suggesting unpredictable absorption. Wiegman et al. (1982) studied intestinal absorption and secretion of radioactive vanadium in Sprague-Dawley rats. Vanadium was administered in a sodium metavanadate form by gavage ($5/\mu\text{mol}$, corresponding to 0.255 mg). After 4 days, ~18% of the dose was excreted in urine and ~69% was recovered in stool. The remainder was retained in various organs and tissues. In an experiment where 1 ml of $\text{Al}(\text{OH})_3$ gel was given to the rats at the same time when vanadium was administered, aluminum hydroxide decreased absorption of vanadium, which was evidenced by decreased urine recovery of vanadium (~8% of administered dose). Stool recovery of vanadium increased to ~86%.

2.2. INHALATION

Several studies have reported that vanadium was identified in the blood, feces and, in most studies, the urine of some, but not all, workers after occupational exposure to vanadium pentoxide dust, indicating that absorption occurred as a result of vanadium pentoxide inhalation (Sjoberg, 1956; Williams, 1952; Vintenner et al., 1955; Lewis, 1959; Zenz and Berg, 1967;

Ross, 1983). Although Vintenner et al. (1955) reported vanadium in the blood of Peruvian workers exposed to high (0.018-58.82 mg V/m³) and low (0.0004-2.116 mg V/m³) exposure levels of vanadium pentoxide to be 0.041 and 0.036 mg/100 cc, respectively, they also detected 0.031 mg/100 cc of vanadium in the blood of the control group of workers who were not occupationally exposed to vanadium pentoxide.

Conklin et al. (1982) reported that 100% of an intratracheal dose of ~0.3 mg V/kg administered as radiolabeled vanadium pentoxide, ⁴⁵V₂O₅, was absorbed by 70-day-old female Fischer rats. The rats were housed in steel metabolism cages and groups of four were killed within 1 hour, within 1/2 day and at 1, 3, 5 and 7 days after ⁴⁵V₂O₅ administration. About 40% of the recovered radioactivity had been cleared from the lungs within 1 hour, and ~90% had been cleared within 3 days. Clearance from the lung was primarily into blood, liver and bone, indicating rapid absorption from this site. By posttreatment day 3, ~40% of the radioactivity had been recovered in the urine. Similar results were obtained for ⁴⁵VO₂Cl.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Dimond et al. (1963) gave human subjects (five females and one male) 25 mg tablets of ammonium vanadyl tartrate up to 4 times/day for 45-68 days. Gastrointestinal difficulties (black, loose stools, increased intestinal activity and cramps) were noted in the treated subjects; however, hematological indices and clinical chemistry were essentially unchanged. Three of the female subjects excreted elevated levels of 17-ketosteroids and 17-hydroxycorticosteroids compared with normal values obtained in this laboratory. Control data was not reported (NIOSH, 1977), and the subjects were given a cholinergic-blocking drug to lessen the gastrointestinal symptoms, which make interpretation of these results difficult.

Franke and Moxon (1937) fed groups of 10 rats of both sexes 25 and 50 ppm vanadium from sodium metavanadate in a wheat diet for 100 days. Controls were given the same diet without added vanadium. Growth rate was depressed in a dose-related manner in both treated groups as compared with controls. Diarrhea occurred in the 50 ppm group. No effect on hemoglobin values was observed. No other parameters of toxicity were evaluated.

Domingo et al. (1985) gave groups of 10 male Sprague-Dawley rats 0, 5, 10 and 50 ppm sodium metavanadate in drinking water for 3 months. Treatment with the compound did not affect food consumption, weight gain, protein utilization, relative organ weights or clinical chemistry indicators of liver function or damage. Slight increases in blood urea and uric acid in the 50 ppm group suggested an alteration in renal function. Histopathological examination was limited to heart, lungs, liver, kidney, spleen, stomach, and small and large intestines of three rats from each group.

"Mild histological changes" consisting of hypertrophy and hyperplasia of the white pulp in the spleen, microhemorrhagic foci in the kidney and infiltration of mononuclear leukocytes in the lungs, mostly in the perivascular regions, occurred in all treated groups, but were most evident at 50 ppm. The investigators concluded that sodium metavanadate was "generally well tolerated" at all concentrations.

Susic and Kentera (1986) gave groups of 15 male Long-Evans rats 0 or 300 ppm ammonium vanadate in the diet for 2 months to measure effects on pulmonary circulation. Body weight, heart rate, mean femoral artery pressure, cardiac output, total peripheral resistance, left ventricular weight and hematocrit values were unaffected. Right ventricular systolic ($p < 0.01$), right ventricular mean pressures ($p < 0.001$) and pulmonary vascular resistance ($p < 0.05$) (the ratio of right ventricular systolic pressure/cardiac output) were statistically significantly increased in treated rats. Right ventricular hypertrophy was evident as increased relative right ventricular weight. The authors concluded that pulmonary hypertension was evident in these rats, with the caveat that the method used to calculate pulmonary vascular resistance (see above) assumes that changes in right ventricular systolic pressure reflect mean pulmonary artery pressure, which may be erroneous.

Groups of five male Wistar rats were treated with vanadium pentoxide at levels of 0, 25 or 50 ppm of dietary vanadium for 35 days, at which time levels were increased to 100 and 150 ppm, respectively, for the two treated groups and continued for an additional 68 days (Mountain et al., 1953). At the end of 103 days, the rats ingesting vanadium pentoxide gained more weight than the control rats, although food consumption was reported to be similar in all groups. There was a decrease in the amount of cystine in the hair of the rats exposed to the high level of vanadium pentoxide. The

amount of cystine in the hair of the rats exposed to the low level of vanadium pentoxide remained nearly constant on average, while the amount of the changes in the cystine content of the hair in treated rats was statistically different from controls. Gross and microscopic examination of the hair revealed structural changes that resembled those observed in cystine-deficient rats. There was a significant decrease in the RBC count and blood hemoglobin concentration of rats exposed to the high level of vanadium pentoxide; these parameters in rats exposed to the low level of vanadium pentoxide were slightly decreased, but significance was not reported.

Gorski and Zaporowska (1983) gave rats ammonium vanadate (200 ppm vanadium) in drinking water and observed decreased body growth, erythrocyte number, hemoglobin concentration and hematocrit after 2 months. After 3 months of vanadium exposure, "all the parameters only had a decreasing tendency." Liver and kidney degeneration was observed in some of the rats. Few details were provided in this brief abstract.

3.1.2. Inhalation. Several reports describe case histories and experimental studies of people exposed to relatively high concentrations of vanadium pentoxide for a short period of time ranging from a few hours to a few days (Musk and Tees, 1982; Zenz et al., 1962; Sjoberg, 1955, Williams, 1952; McTurk et al., 1956; Zenz and Berg, 1967). All developed respiratory symptoms (wheezing, cough, dyspnea), which occurred during exposure or within a few days and usually subsided within 7-14 days; some developed asthma (Musk and Tees, 1982).

In an experiment by Zenz and Berg (1967), two volunteers exposed to 1 mg V_2O_5/m^3 for 8 hours developed symptoms characteristic of vanadium inhalation, including a persistent cough. Upon accidental exposure for 5 minutes to a heavy cloud of vanadium pentoxide dust 3 weeks after the

initial exposure, the same two volunteers developed severe respiratory distress, and coughing continued for a week. In the same study, five volunteers exposed to 0.2 ± 0.06 mg/m³ of vanadium pentoxide for 8 hours developed a cough that lasted 7-10 days. Pulmonary function tests showed no detectable changes after any of these exposures when compared with pre-exposure results.

Sugiura (1978) exposed an unspecified number of rats and mice to 1-2 mg/m³ of vanadium pentoxide for 6 hours/day for 3 months. No effects on growth rate, lung size, blood chemistry or histology were reported in the mice or rats exposed to 0.1-0.4 mg/m³ of vanadium pentoxide. At the higher concentration, however, the rats had a decreased growth rate and enlarged lungs and the mice had thickened alveolar walls and congested lungs. Few details were provided in this brief abstract.

3.2. CHRONIC

3.2.1. Oral. Stokinger et al. (1953) administered dietary vanadium pentoxide to rats at levels of 10 and 100 ppm vanadium for their lifetimes. The criteria used to evaluate the toxicity included hematology, rate of body weight gain and a "fairly comprehensive" histopathological examination (Stokinger, 1985). Except for a reduction in hair cystine content, no significant signs of toxicity in rats were reported. Rats fed 100 ppm exceeded growth of the controls for the first 7 months of the diet. Thereafter, the average group weight was slightly lower than the controls, but more rats survived for longer periods than did the controls.

Schroeder and Mitchener (1975) gave groups of 54 Swiss mice/sex 5 ppm of vanadium metal in the drinking water (added as vanadyl sulfate) for life. Weight measurements showed that the vanadium-treated male mice were significantly heavier than their controls at five out of eight age intervals (30,

60, 90, 180 and 540 days of age). The treated female mice also generally weighed more than their controls throughout the experiment, but the increase was statistically significant only at 540 days of age (the terminal age group). Body weights of males at 540 days were 45.5 vs. 40.6 g for controls, and of females, 43.2 vs. 36.3 g for controls. Male and female mice fed vanadium also had longer lifespans (higher mean age at death) and a statistically significant higher longevity (mean age of last surviving 10%) than controls. In males, the median lifespan and mean longevity of the treated and control mice were 578 vs. 556 days and 880 vs. 763 days, respectively. The values in the treated and control female mice were 620 and 565 days (mean age at death), and 878 and 790 days (mean longevity), respectively. Gross pathological examination for tumors and microscopic examination of "some" sections from the heart, lung, kidneys and spleen following natural death revealed no remarkable compound-related effects.

In a related similarly designed study, 5 ppm vanadium from vanadyl sulfate was added to the drinking water of 52 male and 61 female Long-Evans rats from the time of weaning to natural death (Schroeder et al., 1970). Control groups comprised 52 male and 54 female rats. Growth rate, survival and longevity were found to be similar among the vanadium-treated and control rats. Fasting glucose levels were significantly elevated in the treated female rats, but nonfasting glucose levels were normal in both male and female. Fasting serum cholesterol levels were significantly elevated in treated males and significantly depressed in treated females when compared with respective control values, but the below normal serum cholesterol level in the females may have been related to insufficient levels of dietary chromium. Mean heart weights and mean heart-to-body weight ratios at death showed that the hearts of the treated male rats weighed 4% more than those of controls, but these changes were not found to be significantly different.

Vanadyl sulfate was not found to be tumorigenic, as evidenced by the incidence of grossly visible tumors at necropsy following natural death; and limited histological examinations of the heart, lungs, kidneys, liver and spleen of treated rats were apparently unremarkable.

3.2.2. Inhalation. Sjoberg (1950) presented the case histories of 36 workers (ranging in age from 20-59 years) in a vanadium factory in Sweden who were exposed to vanadium pentoxide at concentrations ranging from 0.05-5.58 mg/m³. Vanadium was detected in the blood and urine of exposed individuals, and some of the workers had developed eczema or a hypersensitivity to vanadium detectable with a skin patch test. Severe respiratory irritation was the most prevalent symptom, but slight changes in blood, hemoglobin concentrations, heart palpitations upon exertion, weakness and neuroasthenic symptoms were observed occasionally. Blood pressure was not increased and there were no gastrointestinal or urinary tract symptoms and no discoloration of the tongue; chronic changes, such as pneumoconiosis, fibrosis or emphysema, were not detected. The short observation period of the Sjoberg (1956) report (~2 years), however, may not have been sufficient to detect chronic effects of vanadium exposure.

Lewis (1959) studied the effects of vanadium pentoxide exposure, usually ranging from 0.010-0.38 mg vanadium/m³, but with one concentration at 0.925 mg vanadium/m³, in 24 men aged 38-60 years. Average duration of exposure was 2.5 years. The control group consisted of 45 men selected at random who were similar to the vanadium-exposed group in age range, economic status and job activity except that they were not occupationally exposed to vanadium. Incidence of respiratory distress (cough, bronchospasm, pulmonary congestion) was increased in vanadium-exposed workers, but there was no

difference in electrocardiograms, hematocrits or clinical urinalyses between the exposed and control groups. The author concluded that there were no permanent effects from chronic vanadium exposure.

Tebrock and Machle (1968) evaluated 250 workers exposed to levels of vanadium pentoxide ranging from 0.02-3.2 mg/m³ (mean=0.844 mg/m³) over an 8-year period. Conjunctivitis, tracheobronchitis and contact dermatitis were the most prevalent clinical observations. No changes in hematology, pulmonary function or blood pressure were noted, although a transient increase in blood pressure was reported in some individuals who did not take proper precautions in areas of high vanadium levels. Tebrock and Machle (1968) concluded that exposure to vanadium pentoxide caused no permanent adverse systemic effects in spite of the observation that there were some chronic changes in the mucus membranes.

Symanski (1939) found severe irritation of the respiratory system and conjunctiva but no adverse systemic effects from chronic exposure to vanadium pentoxide, based on the study of 19 workers exposed to unknown concentrations for a few months to several years. A control group was not provided. According to NIOSH (1977), Symanski (1954) indicated in a follow-up report that emphysema may have resulted from exposure to vanadium pentoxide in two workers during a 9- and a 13-year period.

Vintenner et al. (1955) evaluated three groups of vanadium mining and process workers in Peru who had been employed for 1-10 years. The control group (n=37) was not exposed to vanadium pentoxide in the workplace; the second group (n=39) was exposed to a low level of vanadium pentoxide ranging from 0.004-2.116 mg vanadium/m³; the third group (n=39) was exposed to a high level of vanadium pentoxide ranging from 0.018-58.82 mg vanadium/m³.

The amount of vanadium detected in the blood of workers from whom blood was taken was not reported. Vanadium levels detected in the urine appeared to be significantly higher in the workers occupationally exposed to high levels of vanadium pentoxide. Vanadium levels in the urine from workers exposed to low concentrations of vanadium pentoxide appeared similar to those levels in the urine from controls.

The percentage of workers who complained of cough, chest pain, expectoration, headache, dyspnea, palpitations, tiredness, night sweating and weakness was highest in the group exposed to the high level of vanadium pentoxide, lowest in the control group and intermediate in the group exposed to low levels of vanadium pentoxide (Vintenner et al., 1955). The only complaint more prevalent in the low- than in the high-exposure group was colic. In addition, Vintenner et al. (1955) reported that vanadium pentoxide-exposed workers had more eye complaints, such as itching, swelling and burning sensation, as well as an increased incidence of periodontal disease.

In an epidemiological study, Kiviluoto et al. (1981a) evaluated a group of 63 males (mean age=36.5±9.6 years) who were exposed to vanadium pentoxide in the workplace at time-weighted mean concentrations ranging from 0.012-2.3 mg vanadium/m³ for an average of 10.8 years. The control group consisted of 22 males (mean age=31.9±10.2 years) who were not occupationally exposed to vanadium pentoxide. Analysis of blood and urine samples from 16-18 vanadium pentoxide-exposed workers and of urine samples from 16-17 controls revealed that the serum vanadium concentration was 0.22±0.14 µmol/l (0.011 mg/l) and the urinary vanadium concentration 0.26±0.17 µmol/l (0.013 mg/l) in vanadium pentoxide workers, whereas the urinary vanadium content was less than the detection limit of 0.04 µmol/l (0.002 mg/l) in the controls. Evaluation of blood enzyme levels, blood protein levels,

hematological parameters and WBC counts indicated that there were no vanadium pentoxide-related differences between the exposed and control workers. Although there were statistically significant differences between exposed and control workers for serum albumin, chloride, urea, bilirubin and conjugated bilirubin, Kiviluoto et al. (1981b) indicated that the observed differences were not biologically significant. No evaluation of symptoms (i.e., cough or dyspnea) was presented in this report. No long-term inhalation studies in animals were available.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity and reproductive effects of vanadium and compounds by the oral route could not be located in the available literature; however, Roshchin and Kozimov (1980) observed that 20 daily intraperitoneal injections of 0.85 mg/kg Na_3VO_4 decreased sperm motility and osmotic resistance in rats. Sterility of males and increased mortality of spermatozooids was observed as well. Subcutaneous injection of 0.85 mg/kg/ Na_3VO_4 on day 4 of pregnancy decreased pre-implantation survival by 50%. Carlton et al. (1982) studied the teratogenicity of ammonium vanadate using Syrian golden hamsters. Twenty pregnant hamsters per dose group received 0, 0.47, 1.88 and 3.75 mg/kg of ammonium vanadate by i.p. injection on gestation days 5 through 10. Pregnant females were killed on day 15, opened and uterus was observed for resorption sites and live and dead implantations. All fetuses were removed and observed for malformations. There was a statistically significant increase in skeletal abnormalities and a decrease in the male:female ratio. However, the small number of malformed offspring and the lack of a clear cut dose-response did not allow a definitive assessment of teratogenicity.

3.2.2. Inhalation. Pertinent data regarding the teratogenicity or reproductive effects of vanadium and compounds by inhalation could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Dimond et al. (1963) found that triglyclamol chloride lessened symptoms of gastrointestinal distress in humans given oral doses of ammonium vanadyl tartrate (see Section 3.1.1.). Thompson et al. (1984) observed that feeding rats a "purified diet" with 25 ppm of vanadium as vanadyl sulfate during the postinitiation stages of murine mammary carcinogenesis induced by 1-methyl-1-nitrosourea blocked the carcinogenic response as exhibited by reducing cancer incidence, the average number of cancers/rat and by prolonging the median cancer-free time.

Wright (1968) found that levels of 500-2000 $\mu\text{g/g}$ of chromium in the diet effectively overcame growth depression and mortality in rats fed 20 mg/kg vanadate in the diet.

Ascorbic acid and ethylenediaminetetraacetate were effective as antidotes in experimental vanadium poisonings of mice, rats and dogs (Mitchell and Floyd, 1954). Routes of administration were not specified in the summary of this study (NAS, 1974).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of vanadium and compounds could not be located in the available literature.

4.1.2. Inhalation. In an early epidemiological study of the effects of several industrial pollutants (smoke and some of its components including 3,4-benzopyrene, beryllium, molybdenum, vanadium and arsenic) on cause of death, Stocks (1960) found positive correlations between the incidence of deaths from lung cancer ($r=0.770$) and cancers of other body sites (excluding the stomach) in males ($r=0.556$) and exposure to vanadium in air in 23 localities in Northern England and Wales. When the influence of beryllium and molybdenum were eliminated, however, the correlation coefficient was reduced to 0.347, which is not statistically significant.

4.2. BIOASSAYS

4.2.1. Oral. Administration of 5 ppm vanadium/l (from vanadyl sulfate) to mice and rats in drinking water for life was not tumorigenic; however, histopathological examination was limited (Schroeder and Mitchener, 1975; Schroeder et al., 1970) (see Section 3.2.1.). Schroeder and Balassa (1967) administered 5 mg/l of vanadium as vanadyl sulfate in drinking water to 23 male and 29 female mice. No effects on longevity, histopathology or number of tumors were observed.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled vanadium in animals could not be located in the available literature.

Vanadium pentoxide has been approved by the National Toxicology Program for an inhalation toxicology study (NTP, 1986).

4.3. OTHER RELEVANT DATA

Kanematsu et al. (1980) reported that vanadium pentoxide did not increase the frequency of reverse mutations in the spot test using Escherichia

coli (strains B/r WP2 and WP2) or Salmonella typhimurium (strains TA98, TA100, TA1535, TA1537 and TA1538). However, vanadium pentoxide, ammonium vanadate and VOCl_2 were positive in the rec assay system using a recombination-proficient (H17 Rec⁺) and a recombination-deficient (m45 Rec⁻) strain of Bacillus subtilis at concentrations of 0.5, 0.4 and 0.3 M, respectively (Kada et al., 1980; Kanematsu et al., 1980).

Stoner et al. (1976) investigated the production of lung adenoma in strain A mice following multiple i.p. injections of 13 metallic compounds, including vanadium (III) 2,4-pentanedione; no significant increase in the average number of lung tumors was observed.

4.4. WEIGHT OF EVIDENCE

Although the epidemiology study by Stocks (1960) found a positive correlation between vanadium and other pollutants in industrial pollution and deaths from cancer, particularly lung cancer, when the influence of the pollutants beryllium and molybdenum was removed, the correlation was no longer statistically significant. Since other data on humans are not available to compare with the findings of Stocks (1960), the evidence for carcinogenicity in humans is most appropriately judged to be inadequate.

Three chronic exposure studies were performed using experimental animals. These include a lifetime study in rats with dietary vanadium pentoxide (Stokinger et al., 1953) and lifetime drinking water studies in rats (Schroeder et al., 1970) and mice (Schroeder and Mitchener, 1975) with vanadyl sulfate. The MTD was not approached in any of these experiments, and histopathology evaluation was not comprehensive. The lack of an observed tumorigenic response in these experiments should not be interpreted as a fully valid evaluation for lack of carcinogenicity of ingested vanadium. The carcinogenicity of inhaled vanadium in animals has not been

tested. It is most appropriate, therefore, to consider that existing data are not sufficient to adequately evaluate the carcinogenicity of vanadium in laboratory animals.

IARC has not classified vanadium as to the weight of evidence for carcinogenicity to humans. The EPA weight of evidence classification for vanadium is Group D, not classifiable (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1986a) derived an RfD for vanadium pentoxide of 0.02 mg/kg/day or 1 mg/day for a 70 kg man based on the NOAEL of 35.7 ppm vanadium pentoxide in food associated with decreased hair cystine in a rat chronic oral study (Stokinger et al., 1953). This RfD is erroneous because of a miscalculation in the dose; the RfD for vanadium pentoxide from the Stokinger et al. (1953) study should be 0.009 mg/kg/day, or 0.6 mg/day for a 70 kg human. U.S. EPA (1985b) did not propose an RMCL for vanadium because "preliminary analysis indicated limited potential for drinking water exposure." Vanadium will be considered in later phases of the National Primary Drinking Water Regulations.

ACGIH (1986) recommended a TLV-TWA of 0.05 mg/m³ (as V₂O₅) for respirable dust and fumes based primarily on the findings of Zenz and Berg (1967) who observed coughing and increased mucus in human volunteers exposed to 0.1 mg/m³ vanadium pentoxide dust. NIOSH (1977) recommended a TWA concentration limit of 1 mg/m³ for up to 10 hours/day for a 40-hour work week for vanadium. OSHA (1985) adopted a ceiling of 0.5 mg/m³ and 0.1 mg/m³ for vanadium pentoxide dust and fumes, respectively.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RFD_S)

6.1.1. Oral (RFD_{SO}). Oral exposure to vanadium compounds is associated with increased intestinal activity, cramping (Dimond et al., 1963) and diarrhea (Dimond et al., 1963; Franke and Moxon, 1937), elevated systemic blood pressure, pulmonary hypertension and right ventricular hypertrophy (Susic and Kentera, 1986), disturbed protein assimilation, particularly the sulfur-containing amino acids such as cystine (Domingo et al., 1985; Mountain et al., 1953; Stokinger et al., 1953), reduced kidney function (Domingo et al., 1985), reduced erythrocyte count and blood hemoglobin concentration (Mountain et al., 1953; Franke and Moxon, 1937; Gorski and Zaporowska, 1983) and reduced rate of body weight gain in growing animals (Franke and Moxon, 1937; Gorski and Zaporowska, 1983). The individual studies in humans (Dimond et al., 1963) and most of those in animals (Franke and Moxon, 1937; Susic and Kentera, 1986; Mountain et al., 1953; Gorski and Zaporowska, 1983) do not sufficiently evaluate the endpoints of toxicity associated with vanadium so that any one study may be used with confidence as the basis for an RFD_{SO} for vanadium. The most comprehensive subchronic oral study was performed by Domingo et al. (1985) in which groups of 10 male Sprague-Dawley rats were provided with drinking water containing sodium metavanadate at 0, 5, 10 and 50 ppm for 3 months. By correcting for the atomic weight of vanadium and using body weight and water intake data provided by the investigators (assuming control, low and middle group rat data are identical; actual data provided for controls and high group rats) corresponding vanadium dosages of 0, 0.27, 0.55 and 2.74 mg/kg/day can be estimated. Kidney function appeared to be compromised in the high group as

blood urea nitrogen and uric acid were both elevated. Mild histological lesions were observed in the lungs, kidneys and spleens of all treated animals examined, most noticeably in the high group.

Interpretation of the biological significance of the histopathological lesions caused by sodium metavanadate in rats at vanadium equivalent doses of 0.27 and 0.55 mg/kg/day is complicated by the lack of lesions at comparable doses in lifetime studies with dietary vanadium pentoxide in rats (Stokinger et al., 1953) and drinking water studies with vanadyl sulfate in mice (Schroeder and Mitchener, 1975) and rats (Schroeder et al., 1970). In the dietary study, no histological lesions were observed with vanadium pentoxide at 10 or 100 ppm vanadium (0.5 and 5.0 mg/kg/day, assuming a food factor of 0.05). In the drinking water studies with vanadyl sulfate, no histological lesions in mice or rats were noted at 5 ppm vanadium, the only concentration tested. These concentrations correspond to vanadium dosages of 0.9 mg/kg/day in mice and 0.7 mg/kg/day in rats.

These data suggest that sodium metavanadate may be the more toxic of the vanadium compounds tested. This is consistent with the 100-day study using rats where sodium metavanadate in diet at a vanadium concentration of 25 ppm caused growth retardation and increased mortality (Franke and Moxon, 1937). The conservative approach to risk assessment suggests that an RFD_{SO} for vanadium be derived from the Domingo et al. (1985) experiment with sodium metavanadate, and RFD_{SO} values for other vanadium compounds be derived from applicable studies of these compounds. The middle dose in the Domingo et al. (1985) experiment, corresponding to 0.55 mg vanadium/kg/day is designated a NOAEL, since the investigators concluded that the test compound was "generally well tolerated" at all levels of exposure and because no histopathological lesions were observed with comparable or higher doses of

vanadium in lifetime studies in rats and mice. An RfD_{SO} for vanadium of 0.006 mg/kg/day or 0.4 mg/day for a 70 kg man is derived by application of an uncertainty factor of 100 to the NOAEL of 0.55 mg/kg/day. RfD_{SO} values for sodium metavanadate are 0.01 mg/kg/day or 1.0 mg/day for a 70 kg human. Since no suitable subchronic studies were found for calculation of an RfD_{SO} for vanadium sulfate and vanadium pentoxide, the RfD_0 derived from chronic studies can be adopted as an RfD_{SO} for these compounds.

6.1.2. Inhalation (RfD_{SI}). The subchronic studies summarized in Section 3.1.2. failed to identify NOAELs or LOAELs, or were insufficiently reported to be useful for quantitative risk assessment. An RfD_{SI} for vanadium cannot be derived from the existing data.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). Chronic oral studies with compounds of vanadium include a lifetime dietary study in rats with vanadium pentoxide (10 and 100 ppm vanadium) (Stokinger et al., 1953) and lifetime drinking water studies with vanadyl sulfate (5 ppm vanadium) in mice (Schroeder and Mitchener, 1975) and rats (Schroeder et al., 1970). The only compound-related effects reported were reduced levels of cystine in the hair of rats in the dietary study and minor serum fasting glucose and cholesterol concentration changes in rats in the drinking water studies. Since the biological significance of these observations is doubtful (fasting serum cholesterol was elevated in males and depressed in females), all of these studies identify NOAELs.

An RfD_0 value for vanadium can be obtained from chronic drinking water study with vanadium sulfate in mice (Schroeder and Mitchener, 1975) and rats (Schroeder et al., 1970). A NOAEL of 5 ppm corresponds to vanadium intake of 0.9 mg/kg bw/day in mice and 0.7 mg/kg bw/day in rats. Using an uncertainty factor of 100, one can obtain an RfD_0 of 0.009 mg/kg/day in mice

and 0.007 mg/kg/day in rats. If we adopt a more conservative value in rats, the RfD_0 for vanadium is 0.007 mg/kg/day or 0.5 mg/day for a 70 kg human. The corresponding RfD_0 for vanadium sulfate is 0.02 mg/kg/day or 1.5 mg/day for a 70 kg human. The RfD_0 for vanadium pentoxide can be obtained from chronic dietary study using rats (Stokinger et al., 1953). A NOAEL of 10 ppm of vanadium in diet corresponds to intake in rats of 0.9 mg/kg bw/day of vanadium pentoxide. Using an uncertainty factor of 100, one can calculate an RfD_0 for vanadium pentoxide of 0.009 mg/kg/day or 0.6 mg/day for a 70 kg human. An RfD_0 for sodium vanadate can be obtained from the RfD_{SO} by using an uncertainty factor of 10 to extrapolate from subchronic to chronic exposure for sodium metavanadate. This RfD_0 is then 0.001 mg/kg/day or 0.1 mg/day for a 70 kg human.

CSs have been derived for oral exposure to vanadium pentoxide in two U.S. EPA (1983b, 1985a) analyses and for vanadyl sulfate in one U.S. EPA (1983a) analysis. The largest CS for oral exposure to vanadium pentoxide was 10, based on deaths observed in rats (Stokinger et al., 1953) fed diets containing 2000 ppm vanadium (U.S. EPA, 1983b). For vanadyl sulfate, the highest CS was 3.8 based on minor clinical chemistry changes in rats (Schroeder et al., 1970) exposed to 5 ppm vanadium in their drinking water (U.S. EPA, 1983a). Corresponding CSs for vanadium, based on recalculation of the MEDs corrected for vanadium rather than the compounds, are 10 and 4.5 from vanadium pentoxide and vanadyl sulfate, respectively. A CS can also be derived based on the lesions observed in the lungs, spleens and kidneys of rats exposed to sodium metavanadate in the drinking water associated with a vanadium intake of 0.27 mg/kg/day (Domingo et al., 1985). A body weight of 0.330 kg is estimated from initial body weight and weight gain data provided by the investigators. By applying a correction factor of the cube root of

the ratio of rat to reference human body weight, a human MED of 3.2 mg/day is calculated. No uncertainty factor is applied to expand from subchronic to chronic exposure (see above). The corresponding RV_d is 4.7. An RV_e of 6 is chosen to represent the lesions noted above, resulting in a CS for vanadium of 28.2. The magnitude of the CS for vanadium based on sodium metavanadate, compared with vanadium pentoxide and vanadyl sulfate, reflects the greater toxicity of that compound.

6.2.2. Inhalation (RfD_I). Several human chronic occupational exposure studies were found in the available literature (Symanski, 1939, 1954; Vintenner et al., 1955; Kiviluoto, 1981a,b); however, exposures were not sufficiently quantitated, clinical symptoms were not evaluated, or these studies did not define NOAELs, and consequently they are not useful for quantitative risk assessment.

The ACGIH (1986) TLV of 0.05 mg/m³ for vanadium pentoxide dust and fumes, based upon the studies summarized above, is likewise considered inadequate for the basis of an RfD_I . An RfD_I is not derived because the available data are inadequate.

The U.S. EPA (1985a) derived several CSs for the exposure of humans to atmospheric vanadium pentoxide. The selected CS was 30.1, calculated for persistent cough, dyspnea and wheezing ($RV_e=7$) in humans occupationally exposed to 0.02-3.2 mg/m³ of vanadium pentoxide for 8 years (Tebrock and Machle, 1968). The MED was 6.0 mg/day. A corresponding MED for vanadium is 3.4 mg/day, which corresponds to an RV_d of 4.7 and a CS for vanadium of 32.9. This CS is chosen as most stringently representing the toxicity of inhaled vanadium and indicates the greater toxicity of vanadium by the inhalation route compared with the oral route.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. human oral carcinogenicity data were not available. Animal studies have not shown a carcinogenic response for vanadyl sulfate by the oral route (Schroeder et al., 1970; Schroeder and Mitchener, 1975), although the available data are judged inadequate to properly evaluate the carcinogenic potential in animal test systems. Data were not available for other vanadium compounds; therefore, no q_1^* was derived.

Vanadium pentoxide has been approved for an inhalation toxicology study by the National Toxicology Program (NTP, 1986).

6.3.2. Inhalation. Stocks (1960) suggested that atmospheric exposure to vanadium in combination with other pollutants may be carcinogenic to humans; however, the available data were inadequate to assess the carcinogenic potential by inhalation for vanadium alone.

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APPENDIX

Summary Table for Vanadium and Compounds

Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD) (mg/day)	Reference
Inhalation RfDSI (formerly AIS)	ND	ND	ND	ND
RfDI (formerly AIC)	ND	ND	ND	ND
Oral RfD ₀	3-month exposure to sodium metavanadate in drinking water at 5 ppm (2.1 ppm vanadium) (0.55 mg/kg/day vanadium)	NOAEL: mild lesions in lung, spleen, kidney; impaired kidney function at 50 ppm sodium metavanadate	sodium metavanadate: 0.1	Domingo et al., 1985
rat	lifelong exposure to vanadyl sulfate at 5 ppm of vanadium in drinking water (0.7 mg/kg/day vanadium)	NOAEL: minor serum cholesterol level changes	vanadyl sulfate: 2.0	Schroeder et al., 1970
rat	lifelong exposure to vanadium pentoxide in diet at 10 ppm vanadium (0.9 mg/kg/day of vanadium pentoxide)	NOAEL	vanadium pentoxide: 0.6	Stokinger, 1953

APPENDIX (cont.)

Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD) (mg/day)	Reference
Oral (cont.) RfD ₀				
mouse	lifelong exposure to vanadyl sulfate at 5 ppm of vanadium in drinking water (0.9 mg/kg/day vanadium)	NOAEL; no observed effects	vanadyl sulfate: 1.6	Schroeder and Mitchener, 1975
Maximum CS	human	occupational exposure to vanadium pentoxide at 0.02-3.2 mg/m ³ for 8 years; MED for vanadium of 3.4 mg/day (RV _d =4.7)	CS = 32.9	Tebrock and Machle, 1967

*ND = Not derived because inhalation data were inadequate